T1w/FLAIR-ratio as a predictor for cognition in a large population cohort: Findings from The Maastricht Study

Gerhard S. Drenthen[1,2], Walter H. Backes[1,2], Sebastian Köhler[2,3,4], Miranda T. Schram[2,5], Willemijn J. Jansen[2,3,4], and Jacobus F.A. Jansen[1,2,6]
[1]Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, Netherlands, [2]Mental Health and Neuroscience (MHeNs) Research Institute, Maastricht University, Maastricht, Netherlands, [3]Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, Netherlands, [4]Alzheimer Center Limburg, Maastricht University, Maastricht, Netherlands, [5]Department of Internal Medicine, Maastricht University, Maastricht, Netherlands, [6]Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands

Synopsis

Motivation: Myelin can be a useful predictor of disease progression and cognitive decline, however it requires dedicated MRI sequences. The T1w/FLAIR-ratio, which is more readily available, has previously been introduced as a proxy for the myelin content.

Goal(s): To assess whether the T1w/FLAIR myelin proxy is a better predictor for cognition compared to other established MRI markers (i.e. grey matter volume, white matter hyperintensity load and fractional anisotropy).

Approach: The T1w/FLAIR-ratio is calculated in a large (n=4525) population sample, and predictive value is assessed using linear regression models.

Results: The T1w/FLAIR-ratio is a better predictor of cognitive decline compared to other established MRI-markers.

Impact: The T1w/FLAIR-ratio can be used as a proxy for the myelin content. Here, we showed in a large population-based sample, that the T1w/FLAIR-ratio is a better predictor for cognition compared to atrophy, white matter lesion burden and microstructure.

Introduction

Myelin is a vital element of healthy brain development, and has been previously shown to be lower in patients with mild cognitive impairment and dementia[1]. Moreover, since changes in the white matter even precede the formation of amyloid-beta plaques, demyelination is thought to be an important aspect of the preclinical stages of Alzheimer's disease[2]. Furthermore, a lower myelin content is associated with a steeper cognitive decline[3]. Assessing the myelin content using MRI requires dedicated sequences, which hampers its applicability in large population studies. However, an enhanced myelin contrast can be calculated from standard structural scans, using the ratio of T1w and T2w image intensities[4]. Since FLAIR images are often more readily available, a T1w/FLAIR-ratio was previously proposed[5]. Early detection of cognitive decline using MRI can identify persons at risk for developing dementia, and allows for personalized interventions at an early stage. However, whether this myelin proxy is a better predictor for cognitive decline compared to other established MRI markers (i.e. grey matter volume (GMV), white matter hyperintensities (WMH) load and fractional anisotropy (FA)) has not been studied yet.

Methods

Subjects

We used 4525 participants of The Maastricht Study[6], a population-based cohort study (18% type 2 diabetes (by design), 53% female, aged 59±9 years). The goal of The Maastricht Study is to increase insight into the causes and of chronic disease, with the main focus on diabetes and cardiovascular disease. For each participant, cognitive performance scores were assessed with an extensive neuropsychological test battery with compound scores for the domains of memory, processing speed, and executive function. A global cognition score was calculated by averaging scores across the three domains.

MRI Acquisition

MRI was performed on a 3T MRI (MAGNETOM Prisma-fit, Siemens Healthcare, Erlangen, Germany) using a 64-element head/neck coil. A 3D T1w magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TI/TE 2,300/900/2.98ms, 176 slices, 256×240 matrix size, and 1.00mm cubic voxel size) and a FLAIR sequence (TR/TI/TE 5,000/1,800/394ms, 176 slices, 512×512 matrix size, 0.49×0.49×1.0mm reconstructed voxel size) were acquired. Additionally, diffusion-weighted MRI (dMRI) data were acquired using a diffusion sensitized echo-planar imaging sequence (TR/TE 6100/57ms, 65 slices, 100×100 matrix size, 2.00mm pixel size, 2mm transverse slice thickness, and 64 directions (b=1200s/mm2) and three b=0 scans).

Image analysis

First, both the T1w and FLAIR images were bias-corrected using the N4-ITK bias correction tool[7] . Next, using non-linear histogram calibration the intensity histograms of cerebral tissue (excluding WMH) of the T1w and FLAIR image were matched to the intensity histograms of standard MNI-images[5] using mrhistmatch from MRTrix[8]. Structural scans were automatically segmented into different tissue types (e.g., grey matter, white matter, and WMHs) using SamSeg[9]. Fractional anisotropy was calculated from the dMRI images using the Dipy toolbox[10] after distortion correction using a Synb0-DisCo[11]. The T1w/FLAIR-ratio and FA are averaged over all white matter voxels.

Statistical analysis

To assess whether the T1w/FLAIR-ratio is a better predictor of cognitive decline than GMV, WMH volume and FA, multivariable linear regression models were used. For each model, overall cognition was used as dependent variable, and the four cerebral markers were separately used as independent variables. All models were corrected for age, sex, education level and total intracranial volume. Note that WMH volume was log-transformed. The performance of a predictor was assessed using its t-statistics (β/SE(β)). Next, to statistically test whether the T1w/FLAIR-ratio is a significantly better predictor, distributions of t-statistics are calculated for GMV, WMH-load and FA using bootstrapping with 10,000 samples.

Results

Images of the T1w, FLAIR, T1w/FLAIR-ratio and FA are shown in Figure 1, for a representative subject. Table 1 shows the Pearson's correlation between all pairs of cerebral markers. All the cerebral markers contributed to the prediction of cognition significantly. Regression coefficients for the association of the cerebral markers and cognition are shown in Table 2. Scatter plots of these relationships are shown in Figure 2. The bootstrap analysis revealed that the T1w/FLAIR-ratio has a significantly higher t-statistic compared to GMV ($z=2.68$, $p<.01$) and FA ($z=3.56$, $p<.001$), while the absolute t-statistic for WMH-load was not significantly increased ($z=1.75$, $p=.08$) (Figure 3).

Discussion & Conclusion

The ratio of T1w and T2w contrasts has been previously suggested and applied as a proxy for the myelin content. However, whether this marker is more sensitive compared to other common imaging markers (e.g. atrophy, white matter lesion burden and microstructure) remained unclear. Here, we showed in a large population-based imaging study (The Maastricht Study) that the T1w/FLAIR-ratio is a better predictor for cognition compared to GMV, WMH load and FA. Therefore, the T1w/FLAIR-ratio can be a useful metric to provide predictions of disease progression.

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Figures

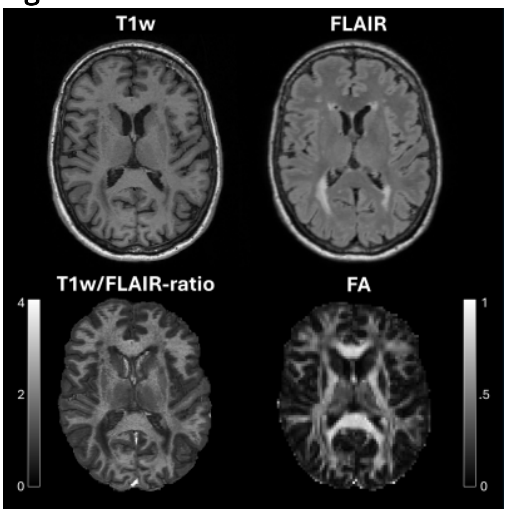


Figure 1: On the top row a T1-weighted (T1w) and FLAIR image are shown, these images are used for the estimation of the gray matter volume and white matter hyperintensity load. On the bottom row the T1w/FLAIR-ratio and fractional anisotropy (FA) are shown. All four images are from a 65 year old female.

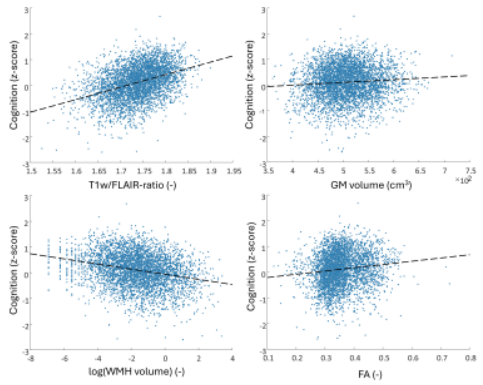


Figure 2: Scatter plots of each cerebral marker with cognition, dashed black line is a least-squares regression line added for visualization. Note that effects of age, sex, education level and total intercranial volume are not included in these figure.

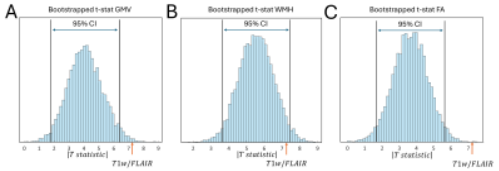


Figure 3: Distributions of the absolute values of t-statistics, obtained using bootstrapping with 10,000 samples for A) grey matter volume, B) white matter intensity load and C) fractional anisotropy. The 95% confidence interval and t-statistic of the T1w/FLAIR-ratio are shown in the figure.

	T1w/FLAIR	GMV	WMH load	FA
T1w/FLAIR	1			
GMV	**.221**	1		
WMH load	**−.499**	**−.068**	1	
FA	**.148**	**.179**	**−.106**	1

Table 1: Correlation matrix indicating the Pearson's correlation coefficient of each cerebral marker pair. All correlations are statistically significant at $p < .001$.

	β	SE(β)	t-statistic	p-value	R-squared
T1w/FLAIR	1.51	.208	7.26	< .001	.286
GMV	$1.34 \cdot 10^{-3}$	$3.23 \cdot 10^{-4}$	4.16	< .001	.280
WMH load	−.030	.005	−5.56	< .001	.282
FA	.562	.135	4.16	< .001	.280

Table 2: Coefficients of the four separate regression models where cognition is predicted from cerebral markers. For each model, the cerebral marker contributes significantly ($p < .001$). The model with the T1w/FLAIR-ratio has the highest R-squared (i.e. explains the most variance in the data). Note that for all regression models age, sex, education level and total intracranial volume are added as covariates (these coefficients are not shown).